

**RIBAVIRIN - ribavirin capsule**  
**Aurobindo Pharma Limited**

-----

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ribavirin capsules safely and effectively. See full prescribing information for ribavirin capsules.

**RIBAVIRIN capsules USP, for oral use**

**Initial U.S. Approval: 1998**

**WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS**

*See full prescribing information for complete boxed warning.*

- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C (5.10).**
- **The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin (2.4, 5.2).**
- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy (4, 5.1, 8.1, 13.1, 17).**

----- **RECENT MAJOR CHANGES** -----

Usage Safeguards (5.10)

05/2015

----- **INDICATIONS AND USAGE** -----

Ribavirin capsules USP are a nucleoside analogue indicated in combination with interferon alfa-2b (nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (1.1)

Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

----- **DOSAGE AND ADMINISTRATION** -----

Ribavirin capsules are administered according to body weight. (2.2)

Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction. (2.4, 12.3)

----- **DOSAGE FORMS AND STRENGTHS** -----

Ribavirin Capsules 200 mg (3)

----- **CONTRAINDICATIONS** -----

- Pregnant women and men whose female partners are pregnant (4, 8.1)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (4)
- Autoimmune hepatitis (4)
- Hemoglobinopathies (4)
- Creatinine clearance less than 50 mL/min (4)
- Coadministration with didanosine (4, 7.1)

----- **WARNINGS AND PRECAUTIONS** -----

- **Pregnancy Category X (5.1, 8.1, 8.3)**
  - Birth defects and fetal death with ribavirin: Patients must have a negative pregnancy test prior to therapy; use at least 2 forms of contraception and undergo monthly pregnancy tests.

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Monotherapy with ribavirin is not permitted. (5.10)
- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (5.2)
- Pancreatitis. (5.3)
- Pulmonary infiltrates or pulmonary function impairment. (5.4)

- New or worsening ophthalmologic disorders. (5.5)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities. (5.6)
- Dental/periodontal disorders reported with combination therapy. (5.7)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.9)

#### ----- ADVERSE REACTIONS -----

Most common adverse reactions (approximately 40%) in adult patients receiving ribavirin/INTRON A combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (6.2)

**To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### ----- DRUG INTERACTIONS -----

Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (7.2)

#### ----- USE IN SPECIFIC POPULATIONS -----

- Nursing mothers: Potential adverse reactions from the drug in nursing infants. (8.1, 8.3)
- Pediatrics: Safety and efficacy in patients less than 3 years old have not been established. (8.4)
- Organ transplant recipients: Safety and efficacy not studied. (8.6)
- Co-infected Patients: Safety and efficacy with HIV or HBV co-infection have not been established. (8.7)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 7/2015**

---

## **FULL PRESCRIBING INFORMATION: CONTENTS\***

### **WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS**

#### **1 INDICATIONS AND USAGE**

- 1.1 Chronic Hepatitis C (CHC)

#### **2 DOSAGE AND ADMINISTRATION**

- 2.2 Ribavirin/INTRON A Combination Therapy
- 2.3 Laboratory Tests
- 2.4 Dose Modifications

#### **3 DOSAGE FORMS AND STRENGTHS**

#### **4 CONTRAINDICATIONS**

#### **5 WARNINGS AND PRECAUTIONS**

- 5.1 Pregnancy
- 5.2 Anemia
- 5.3 Pancreatitis
- 5.4 Pulmonary Disorders
- 5.5 Ophthalmologic Disorders
- 5.6 Laboratory Tests
- 5.7 Dental and Periodontal Disorders
- 5.9 Impact on Growth - Pediatric Use
- 5.10 Usage Safeguards

#### **6 ADVERSE REACTIONS**

- 6.2 Clinical Trials Experience - Ribavirin/INTRON A Combination Therapy
- 6.3 Postmarketing Experiences

#### **7 DRUG INTERACTIONS**

- 7.1 Didanosine
- 7.2 Nucleoside Analogues
- 7.3 Drugs Metabolized by Cytochrome P-450
- 7.4 Azathioprine

#### **8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Organ Transplant Recipients
- 8.7 HIV or HBV Co-infection

## **10 OVERDOSAGE**

## **11 DESCRIPTION**

## **12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

## **13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and Pharmacology

## **14 CLINICAL STUDIES**

- 14.2 Ribavirin/INTRON A Combination Therapy

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

## **17 PATIENT COUNSELING INFORMATION**

\* Sections or subsections omitted from the full prescribing information are not listed.

---

## **FULL PRESCRIBING INFORMATION**

### **WARNING: RISK OF SERIOUS DISORDERS AND RIBAVIRIN-ASSOCIATED EFFECTS**

- Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication [see *Warnings and Precautions* (5.10)].
- The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin [see *Dosage and Administration* (2.4), and *Warnings and Precautions* (5.2)].
- Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period [see *Contraindications* (4), *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1), *Nonclinical Toxicology* (13.1) and *Patient Counseling Information* (17)].

## **1 INDICATIONS AND USAGE**

### **1.1 Chronic Hepatitis C (CHC)**

Ribavirin capsules USP in combination with interferon alfa-2b (nonpegylated) are indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease [see *Warnings and Precautions* (5.9,5.10), and *Use in Specific Populations* (8.4)].

The following points should be considered when initiating ribavirin capsules USP combination therapy

with INTRON A®:

- These indications are based on achieving undetectable HCV-RNA after treatment for 24 or 48 weeks and maintaining a Sustained Virologic Response (SVR) 24 weeks after the last dose.
- Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, significant bridging fibrosis or cirrhosis, and genotype 1 infection [see *Clinical Studies (14)*].
- No safety and efficacy data are available for treatment of longer than one year.

## 2 DOSAGE AND ADMINISTRATION

Under no circumstances should ribavirin capsules be opened, crushed, or broken. Ribavirin capsules should be taken with food [see *Clinical Pharmacology (12.3)*]. Ribavirin capsules should not be used in patients with creatinine clearance less than 50 mL/min.

### 2.2 Ribavirin/INTRON A Combination Therapy

#### **Adults**

##### Duration of Treatment – Interferon Alpha-naïve Patients

The recommended dose of INTRON A is 3 million IU three times weekly subcutaneously. The recommended dose of ribavirin capsules depends on the patient's body weight (refer to **Table 3**). The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen [see *Indications and Usage (1.1)*, and *Clinical Studies (14)*]. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

##### Duration of Treatment – Re-treatment with INTRON A/Ribavirin in Relapse Patients

In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

**Table 3: Recommended Dosing**

<b>Body Weight</b>	<b>Ribavirin Capsules</b>
≤75 kg	2 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally
>75 kg	3 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally

#### **Pediatrics**

The recommended dose of ribavirin capsules is 15 mg/kg per day orally (divided dose AM and PM). INTRON A for Injection by body weight of 25 kg to 61 kg is 3 million IU/m<sup>2</sup> three times weekly subcutaneously.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24

weeks.

### 2.3 Laboratory Tests

The following laboratory tests are recommended for all patients treated with ribavirin capsules, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate [see *Warnings and Precautions* (5.2, 5.7)]), complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG [see *Warnings and Precautions* (5.2)].

### 2.4 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during combination ribavirin/INTRON A therapy, modify, or discontinue the dose until the adverse reaction abates or decreases in severity [see *Warnings and Precautions* (5)]. If intolerance persists after dose adjustment, combination therapy should be discontinued.

Ribavirin capsules should not be used in patients with creatinine clearance less than 50 mL/min. Patients with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia [see *Warnings and Precautions* (5.2), *Use in Specific Populations* (8.5), and *Clinical Pharmacology* (12.3)].

Ribavirin capsules should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped [see *Warnings and Precautions* (5.2)].

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by greater than or equal to 2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains less than 12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin capsules dose modified or discontinued per **Table 4** [see *Warnings and Precautions* (5.2)].

**Table 4: Guidelines for Dose Modification and Discontinuation of Ribavirin in combination with INTRON A Based on Laboratory Parameters in Adults and Pediatrics**

Laboratory Parameters	Reduce Ribavirin Daily Dose (see note 1) if:	Reduce INTRON A Dose (see note 2) if:	Discontinue Therapy if:
WBC	N/A	1 to $<1.5 \times 10^9/L$	$<1 \times 10^9/L$
Neutrophils	N/A	0.5 to $<0.75 \times 10^9/L$	$<0.5 \times 10^9/L$
Platelets	N/A	25 to $<50 \times 10^9/L$ (adults)	$<25 \times 10^9/L$ (adults)
	N/A	50 to $<70 \times 10^9/L$ (pediatrics)	$<50 \times 10^9/L$ (pediatrics)
Creatinine	N/A	N/A	$>2$ mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	8.5 to $<10$ g/dL	N/A	$<8.5$ g/dL
Reduce Ribavirin Dose by 200			

	<b>mg/day and INTRON A Dose by Half if:</b>	
Hemoglobin in patients with history of stable cardiac disease <sup>*†</sup>	≥2 g/dL decrease in hemoglobin during any four week period during treatment	<8.5 g/dL or <12 g/dL after four weeks of dose reduction

Note 1: *Adult patients:* 1<sup>st</sup> dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2<sup>nd</sup> dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

*Pediatric patients:* 1<sup>st</sup> dose reduction of ribavirin is to 12 mg/kg/day, 2<sup>nd</sup> dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: *For patients on ribavirin/INTRON A combination therapy:* reduce INTRON A dose by 50%.

\* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease.

Refer to labeling for INTRON A for additional information about how to reduce an INTRON A dose.

### 3 DOSAGE FORMS AND STRENGTHS

**Ribavirin Capsules, 200 mg** are white/white, size ‘1’ hard gelatin capsule filled with white to off-white granular powder and imprinted with ‘E’ on white cap and ‘81’ on white body with black ink.

### 4 CONTRAINDICATIONS

Ribavirin capsules combination therapy is contraindicated in:

- women who are pregnant. Ribavirin capsules may cause fetal harm when administered to a pregnant woman. Ribavirin capsules are contraindicated in women who are or may become pregnant. If ribavirin capsules are used during pregnancy, or if the patient becomes pregnant while taking ribavirin capsules, the patient should be apprised of the potential hazard to her fetus [see *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1) and *Patient Counseling Information* (17)]
- men whose female partners are pregnant
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min. [see *Use in Specific Populations* (8.5) and *Clinical Pharmacology* (12.3)]
- Coadministration of ribavirin capsules and didanosine is contraindicated because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in patients receiving didanosine in combination with ribavirin [see *Drug Interactions* (7.1)].

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Pregnancy

**Ribavirin capsules may cause birth defects and death of the unborn child. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use at least two forms of contraception and**

**have monthly pregnancy tests during treatment and during the 6-month period after treatment has been stopped.** Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy [see *Boxed Warning*, *Contraindications* (4), *Use in Specific Populations* (8.1), and *Patient Counseling Information* (17)].

## **5.2 Anemia**

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of ribavirin/INTRON A-treated subjects in clinical trials. The anemia associated with ribavirin capsules occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained before the start of treatment and at Week 2 and Week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate [see *Dosage and Administration* (2.4)].

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued [see *Dosage and Administration* (2.4)]. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

## **5.3 Pancreatitis**

Ribavirin and INTRON A therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

## **5.4 Pulmonary Disorders**

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during therapy with ribavirin with alpha interferon combination therapy; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination therapy should be discontinued.

## **5.5 Ophthalmologic Disorders**

Ribavirin is used in combination therapy with alpha interferons. Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein, thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, and serous retinal detachment are induced or aggravated by treatment with alpha interferons. All patients should receive an eye examination at baseline. Patients with pre-existing ophthalmologic disorders (e.g., diabetic or hypertensive retinopathy) should receive periodic ophthalmologic exams during combination therapy with alpha interferon treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Combination therapy with alpha interferons should be discontinued in patients who develop new or worsening ophthalmologic disorders.

## **5.6 Laboratory Tests**

In the adult clinical trial, complete blood counts (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at Weeks 2, 4, 8, 12, and then at 6-week intervals, or more frequently if abnormalities developed.

In pediatric subjects, the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment Week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment [see *Dosage and Administration* (2)].

## 5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and nonpegylated interferon alfa-2b. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, they should be advised to rinse out their mouth thoroughly afterwards.

## 5.9 Impact on Growth - Pediatric Use

An impact on growth was seen in subjects after treatment with ribavirin and INTRON A combination therapy for one year. In a long-term follow-up trial of a limited number of these subjects, combination therapy resulted in reduced final adult height in some subjects [see *Adverse Reactions* (6.2)].

## 5.10 Usage Safeguards

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, ribavirin capsules must not be used alone. The safety and efficacy of ribavirin capsules have only been established when used together with INTRON A as combination therapy.

The safety and efficacy of ribavirin/INTRON A therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin capsules should not be used for these indications. Ribavirin for inhalation has separate labeling, which should be consulted if ribavirin inhalation therapy is being considered.

There are significant adverse reactions caused by ribavirin/INTRON A therapy, including severe depression and suicidal or homicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. Labeling for INTRON A should be reviewed in their entirety for additional safety information prior to initiation of combination treatment.

## 6 ADVERSE REACTIONS

Clinical trials with ribavirin in combination with INTRON A have been conducted in over 7800 subjects.

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients [see *Warnings and Precautions* (5.2)].

Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving INTRON A in combination with ribavirin were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving ribavirin in combination with INTRON A were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

The Adverse Reactions section references the following clinical trials:

- Ribavirin/INTRON A Combination Therapy trials for adults and pediatrics.



Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

## 6.2 Clinical Trials Experience - Ribavirin/INTRON A Combination Therapy

### Adult Subjects

In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-related adverse reactions that occurred in the U.S. trials with greater than or equal to 5% incidence are provided by treatment group (see **Table 9**). In general, the selected treatment-related adverse reactions were reported with lower incidence in the international trials as compared to the U.S. trials, with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

### Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with greater than or equal to 5% incidence among all pediatric subjects who received the recommended dose of ribavirin/INTRON A combination therapy are provided in **Table 9**.

**Table 9: Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects**

Subjects Reporting Adverse Reactions*	Percentage of Subjects						
	U.S. Previously Untreated Study				U.S. Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=231)	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=225)	INTRON A/Ribavirin (N=77)	INTRON A/Placebo (N=76)	INTRON A/Ribavirin (N=118)
<b>Application Site Disorders</b>							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
<b>Body as a Whole - General Disorders</b>							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
<b>Central &amp; Peripheral Nervous System Disorders</b>							
Dizziness	17	15	23	19	26	21	20
<b>Gastrointestinal System Disorders</b>							
Nausea	38	35	46	33	47	33	33

Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
<b>Musculoskeletal System Disorders</b>							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal Pain	20	26	28	32	22	28	21
<b>Psychiatric Disorders</b>							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
<b>Respiratory System Disorders</b>							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
<b>Skin and Appendages Disorders</b>							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
<b>Special Senses, Other Disorders</b>							
Taste Perversion	7	4	8	4	6	5	<1

\* Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24-week post-treatment period. Long-term data in a limited number of patients, however, suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients [see *Warnings and Precautions* (5.9)].

### Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (see **Table 10**).

**Hemoglobin.** Hemoglobin decreases among subjects receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects treated for 48 weeks, the mean maximum decrease from baseline was 3.1 g/dL in the U.S. trial and 2.9 g/dL in the international trial. In relapse subjects, the mean maximum decrease from baseline was 2.8 g/dL in the U.S. trial and 2.6 g/dL in the international trial. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most subjects.

**Bilirubin and Uric Acid.** Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurred most frequently in subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

**Table 10: Selected Laboratory Abnormalities During Treatment With Ribavirin and INTRON A: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects**

	Percentage of Subjects
--	------------------------

	U.S. Previously Untreated Study				U.S. Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
<b>Hemoglobin (g/dL)</b>							
9.5 to 10.9	24	1	32	1	21	3	24
8 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
< 6.5	0	0	0	0	0	0	0
<b>Leukocytes (x 10<sup>9</sup>/L)</b>							
2 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1 to 1.4	0.9	0	2	0	0	0	0
< 1	0	0	0	0	0	0	0
<b>Neutrophils (x 10<sup>9</sup>/L)</b>							
1 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
<b>Platelets (x 10<sup>9</sup>/L)</b>							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
<b>Total Bilirubin (mg/dL)</b>							
1.5 to 3	27	13	32	13	21	7	2
3.1 to 6	0.9	0.4	2	0	3	0	0
6.1 to 12	0	0	0.4	0	0	0	0
>12	0	0	0	0	0	0	0

### 6.3 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of ribavirin in combination with INTRON A. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

#### *Blood and Lymphatic System disorders*

Pure red cell aplasia, aplastic anemia

#### *Ear and Labyrinth disorders*

Hearing disorder, vertigo

#### *Respiratory, Thoracic and Mediastinal disorders*

Pulmonary hypertension

## *Eye disorders*

Serous retinal detachment

## *Endocrine disorders*

Diabetes

## **7 DRUG INTERACTIONS**

### **7.1 Didanosine**

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of ribavirin capsules and didanosine is contraindicated. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

### **7.2 Nucleoside Analogues**

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Adding treatment with alpha interferons alone or in combination with ribavirin may increase the risk in this patient population. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate (*see labeling for individual NRTI product*). Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Ribavirin may antagonize the cell culture antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine, and zidovudine, which could lead to decreased antiretroviral activity.

### **7.3 Drugs Metabolized by Cytochrome P-450**

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A and ribavirin capsules in a multiple-dose pharmacokinetic study.

### **7.4 Azathioprine**

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary.

## **8 USE IN SPECIFIC POPULATIONS**

## 8.1 Pregnancy

### Teratogenic Effects

#### ***Pregnancy Category X***

*[See Contraindications (4), Warnings and Precautions (5.1), and Nonclinical Toxicology (13.1)].*

#### ***Treatment and Post-treatment:***

##### **Potential Risk to the Fetus:**

Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14 to 28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 times the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months post-therapy based on a multiple-dose half-life ( $t_{1/2}$ ) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with ribavirin and for the 6-month post-therapy period (e.g., 15 half-lives for ribavirin clearance from the body).

**A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for 6 months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.**

## 8.3 Nursing Mothers

It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin.

## 8.4 Pediatric Use

For treatment with ribavirin/INTRON A, evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed.

Long-term follow-up data in pediatric subjects indicates that ribavirin in combination with INTRON A may induce a growth inhibition that results in reduced height in some patients *[see Warnings and Precautions (5.9) and Adverse Reactions (6.2)]*.

**Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs. 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)]*.** As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia *[see Warnings and Precautions (5.2)]*.

## 8.5 Geriatric Use

Clinical trials of ribavirin/INTRON A therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min [see *Contraindications (4)*].

In general, ribavirin capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than younger patients (28%) [see *Warnings and Precautions (5.2)*].

## 8.6 Organ Transplant Recipients

The safety and efficacy of INTRON A alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

## 8.7 HIV or HBV Co-infection

The safety and efficacy of INTRON A/ribavirin for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

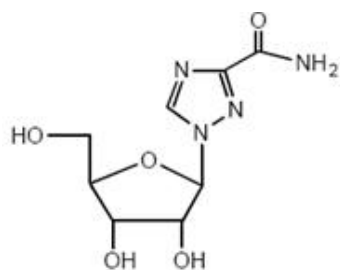
## 10 OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 g of ribavirin capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or ribavirin overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

## 11 DESCRIPTION

Ribavirin, is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula (see **Figure 1**).



**Figure 1: Structural Formula**

Ribavirin USP is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The molecular formula is  $C_8H_{12}N_4O_5$  and the molecular weight is 244.21.

Ribavirin capsules USP consist of a white to off-white granular powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ribavirin is an antiviral agent [see Microbiology (12.4)].

### 12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in **Table 11**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and  $AUC_{tf}$  (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and  $C_{max}$  was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on  $AUC_{12hr}$ , a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

#### ***Effect of Antacid on Absorption of Ribavirin:***

Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin  $AUC_{tf}$ . The clinical relevance of results from this single-dose study is unknown.

**Table 11: Mean (% CV) Pharmacokinetic Parameters for Ribavirin When Administered Individually to Adults**

Parameter	Ribavirin		
	Single-Dose 600 mg Oral Solution (N=14)	Single-Dose 600 mg Capsules (N=12)	Multiple-Dose 600 mg Capsules twice daily (N=12)
$T_{max}$ (hr)	1 (34)	1.7 (46)*	3 (60)
$C_{max}$ (ng/mL)	872 (42)	782 (37)	3680 (85)
$AUC_{tf}$ (ng.hr/mL)	14,098 (38)	13,400 (48)	228,000 (25)
$T_{1/2}$ (hr)		43.6 (47)	298 (30)
Apparent Volume of		2825 (9) <sup>†</sup>	

Distribution (L)			
Apparent Clearance (L/hr)		38.2 (40)	
Absolute Bioavailability		64% (44) <sup>‡</sup>	

\* N=11.

† Data obtained from a single-dose pharmacokinetic study using <sup>14</sup>C labeled ribavirin; N=5.

‡ N=6.

### ***Tissue Distribution:***

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e<sub>s</sub>-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

### ***Metabolism and Excretion:***

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of <sup>14</sup>C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

### ***Special Populations:***

#### **Renal Dysfunction**

The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC<sub>tf</sub> value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance greater than 90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC<sub>tf</sub> was twofold greater when compared to control subjects. The increased AUC<sub>tf</sub> appears to be due to reduction of renal and nonrenal clearance in these subjects. Phase 3 efficacy trials included subjects with creatinine clearance values greater than 50 mL/min. The multiple-dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance less than 50 mL/min should not be treated with ribavirin [see *Contraindications (4)*].

#### **Hepatic Dysfunction**

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC<sub>tf</sub> values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C<sub>max</sub> values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

#### **Elderly Patients**

Pharmacokinetic evaluations in elderly subjects have not been performed.

#### **Gender**

There were no clinically significant pharmacokinetic differences noted in a single-dose trial of 18 male and 18 female subjects.

#### **Pediatric Patients**



Multiple-dose pharmacokinetic properties for ribavirin capsules and INTRON A in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 12**. The pharmacokinetics of ribavirin and INTRON A (dose-normalized) are similar in adults and pediatric subjects.

Complete pharmacokinetic characteristics of ribavirin oral solution have not been determined in pediatric subjects. Ribavirin  $C_{min}$  values were similar following administration of ribavirin oral solution or ribavirin capsules during 48 weeks of therapy in pediatric subjects (3 to 16 years of age).

**Table 12: Mean (% CV) Multiple-dose Pharmacokinetic Parameters for INTRON A and Ribavirin Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C**

Parameter	RIBAVIRIN 15 mg/kg/day as 2 divided doses (N=17)	INTRON A 3 MIU/m <sup>2</sup> three times weekly (N=54)
T <sub>max</sub> (hr)	1.9 (83)	5.9 (36)
C <sub>max</sub> (ng/mL)	3275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent Clearance L/hr/kg	0.27 (27)	ND <sup>†</sup>

\* AUC<sub>12</sub> (ng•hr/mL) for ribavirin; AUC<sub>0-24</sub> (IU•hr/mL) for INTRON A.

† ND=not done.

Note: numbers in parenthesis indicate % coefficient of variation.

#### Effect of Food on Absorption of Ribavirin

Both AUC<sub>0-12</sub> and C<sub>max</sub> increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study [see Dosage and Administration (2)].

## 12.4 Microbiology

### **Mechanism of Action**

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in tissue culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

### **Antiviral Activity in Cell Culture**

The antiviral activity of ribavirin in the HCV-replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct antiviral activity has been observed in tissue culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell containing self-replicating HCV-RNS (HCV replicon cells) or HCV infection.

### **Cross-resistance**

There is no reported cross-resistance between non-pegylated interferons and ribavirin.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### **Carcinogenesis**

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic

p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was noncarcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult).

### ***Mutagenesis***

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

### ***Impairment of Fertility***

Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no-effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 times the maximum recommended human 24-hour dose of ribavirin) [see *Contraindications* (4), and *Warnings and Precautions* (5.1)].

Fertile women and partners of fertile women should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple-dose half-life ( $t_{1/2}$ ) of ribavirin of 12 days, effective contraception must be utilized for 6 months post-therapy (e.g., 15 half-lives of clearance for ribavirin).

Ribavirin should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1 to 0.8 times the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

## **13.2 Animal Toxicology and Pharmacology**

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively (estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times the maximum human 24-hour dose of ribavirin)] have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Days 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

## 14 CLINICAL STUDIES

### 14.2 Ribavirin/INTRON A Combination Therapy

#### Adult Subjects

##### Previously Untreated Subjects

Adults with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for subjects weighing less than or equal to 75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The international trial did not contain a 24-week INTRON A and placebo treatment arm. The U.S. trial enrolled 912 subjects who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 799 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Trial results are summarized in **Table 18**.

**Table 18: Virologic and Histologic Responses: Previously Untreated Subjects\***

	U.S. Trial				International Trial		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A/ Ribavirin(N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin(N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin(N=265)	INTRON A/ Ribavirin(N=268)	INTRON A/ Placebo (N=266)
<b>Virologic Response</b>							
Responder <sup>†</sup>	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
<b>Histologic Response</b>							
Improvement <sup>‡</sup>	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

\* Number (%) of subjects.

<sup>†</sup> Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

<sup>‡</sup> Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of ribavirin/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among subjects with HCV Genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV-RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for subjects with HCV non-genotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

##### Relapse Subjects

Subjects with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central

laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin 1200 mg/day (1000 mg/day for subjects weighing  $\leq 75$  kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The U.S. trial enrolled 153 subjects who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 192 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Trial results are summarized in **Table 19**.

**Table 19: Virologic and Histologic Responses: Relapse Subjects\***

	U.S. Trial		International Trial	
	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=96)	INTRON A/ Placebo (N=96)
<b>Virologic Response</b>				
Responder <sup>†</sup>	33 (43)	3 (4)	46 (48)	5 (5)
Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
<b>Histologic Response</b>				
Improvement <sup>‡</sup>	38 (49)	27 (36)	49 (51)	30 (31)
No improvement	23 (30)	37 (49)	29 (30)	44 (46)
Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

\* Number (%) of subjects.

<sup>†</sup> Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

<sup>‡</sup> Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse trials.

### ***Pediatric Subjects***

Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with ribavirin 15 mg/kg per day and INTRON A 3 MIU/m<sup>2</sup> three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment, of which 57% were male, 80% Caucasian, and 78% genotype 1. Subjects less than 5 years of age received ribavirin oral solution and those 5 years of age or older received either ribavirin oral solution or capsules.

Trial results are summarized in **Table 20**.

**Table 20: Virologic Response: Previously Untreated Pediatric Subjects\***

	INTRON A 3 MIU/m <sup>2</sup> three times weekly/ Ribavirin 15 mg/kg/day
Overall Response <sup>†</sup> (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

\* Number (%) of subjects.

<sup>†</sup> Defined as HCV-RNA below limit of detection using a research-based RT - PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/ribavirin combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

**Ribavirin Capsules USP, 200 mg** are white/white, size ‘1’ hard gelatin capsule filled with white to off-white granular powder and imprinted with ‘E’ on white cap and ‘81’ on white body with black ink.

Bottles of 42	NDC 65862-290-42
Bottles of 56	NDC 65862-290-56
Bottles of 70	NDC 65862-290-70
Bottles of 84	NDC 65862-290-84
Bottles of 180	NDC 65862-290-18
Bottles of 500	NDC 65862-290-05

**Store** at 20° to 25° C (68° to 77° F); excursions permitted to 15° to 30° C (59° to 86° F) [ see USP Controlled Room Temperature] .

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-Approved Patient Labeling (Medication Guide).

### **Anemia**

The most common adverse experience occurring with ribavirin capsules is anemia, which may be severe [see *Warnings and Precautions (5.2) and Adverse Reactions (6)*]. Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter [see *Dosage and Administration (2.3)*]. It is advised that patients be well hydrated, especially during the initial stages of treatment.

### **Pregnancy**

Patients must be informed that ribavirin capsules may cause birth defects and death of the unborn child. Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking ribavirin. Ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months post therapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin and for 6 months post therapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy [see *Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1)*].

If pregnancy does occur during treatment or during 6 months post therapy, the patient must be advised of the teratogenic risk of ribavirin therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Prescribers should report such cases by calling 1-800-593-2214.

### **Risks versus Benefits**

Patients receiving ribavirin capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be

informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

Patients should be informed about what to do in the event they miss a dose of ribavirin; the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Patients should be advised to contact their healthcare provider if they have questions.

Intron A is a registered trademark of Schering Corporation.

## **MEDICATION GUIDE**

### **Ribavirin Capsules USP**

(rye" ba vye' rin)

Read this Medication Guide before you start taking ribavirin capsules, and each time you get a refill. There may be new information. This information does not take the place of talking to your health care provider about your medical condition or your treatment.

#### **What is the most important information I should know about ribavirin capsules?**

- 1. Do Not take ribavirin capsules alone to treat chronic hepatitis C infection. Ribavirin capsules should be used in combination with interferon alfa-2b (Intron® A) to treat chronic hepatitis C infection.**
- 2. Ribavirin capsules may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of Heart Problems, and in rare cases can cause a Heart Attack and Death. Tell your health care provider if you have ever had any heart problems. Ribavirin capsules may not be right for you. Seek medical attention right away if you experience chest pain.**
- 3. Ribavirin capsules may cause Birth Defects or the Death of your unborn baby. Do Not Take ribavirin capsules if you or your sexual partner is pregnant or plan to become pregnant. Do Not become Pregnant within 6 months after discontinuing ribavirin capsules therapy.** You must use 2 forms of birth control when you take ribavirin capsules and for the 6 months after treatment.
  - Females must have a pregnancy test before starting ribavirin capsules, every month while taking ribavirin capsules, and every month for the 6 months after the last dose of ribavirin capsules.
  - **If you or your female sexual partner becomes pregnant while taking ribavirin capsules or within 6 months after you stop taking ribavirin capsules, tell your health care provider right away. You or your health care provider should contact the ribavirin pregnancy registry by calling 1-800-593-2214. The ribavirin pregnancy registry collects information about what happens to mothers and their babies if the mother takes ribavirin capsules while she is pregnant.**

#### **What are ribavirin capsules?**

Ribavirin capsules are a medicine used with interferon alfa-2b (Intron A) to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.

It is not known if ribavirin capsules use for longer than 1 year is safe and will work.

It is not known if ribavirin capsules use in children younger than 3 years old is safe and will work.

#### **Who should not take ribavirin capsules?**

See “What is the most important information I should know about ribavirin capsules?”

**Do not take ribavirin capsules if you have:**

- or ever had serious allergic reactions to the ingredients in ribavirin capsules. See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- taken or currently take didanosine (VIDEX®).

Talk to your health care provider before taking ribavirin capsules if you have any of these conditions.

**What should I tell my health care provider before taking ribavirin capsules?****Before you take ribavirin capsules, tell your health care provider if you have or ever had:**

- treatment for hepatitis C that did not work for you.
- breathing problems. Ribavirin capsules may cause or worsen breathing problems you already have.
- vision problems. Ribavirin capsules may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with ribavirin capsules.
- certain blood disorders such as anemia (low red blood cell count).
- high blood pressure, heart problems, or have had a heart attack. Your health care provider should check your blood and heart before you start treatment with ribavirin capsules.
- thyroid problems.
- liver problems other than hepatitis C infection.
- human immunodeficiency virus (HIV) or any immunity problems.
- mental health problems, including depression and thoughts of hurting yourself or others.
- kidney problems.
- an organ transplant.
- diabetes. Ribavirin capsules may make your diabetes worse or harder to treat.
- any other medical condition.
- are breastfeeding. It is not known if ribavirin passes into your breast milk. You and your health care provider should decide if you will take ribavirin capsules or breastfeed.

**Tell your health care provider about all the medicines you take**, including prescription medicines, vitamins, and herbal supplements. Ribavirin capsules may affect the way other medicines work.

**Especially tell your health care provider if you take didanosine (VIDEX®) or azathioprine (Imuran and Azasan).**

Know the medicines you take. Keep a list of them to show your health care provider or pharmacist when you get a new medicine.

**How should I take ribavirin capsules?**

- Take ribavirin capsules exactly as your health care provider tells you. Your health care provider will tell you how much ribavirin capsules to take and when to take them.
- Take ribavirin capsules with food.
- Take **ribavirin capsules** whole. Do not open, break, or crush **ribavirin capsules** before swallowing. If you cannot swallow **ribavirin capsules** whole, tell your health care provider.
- If you miss a dose of ribavirin capsules, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your health care provider.
- If you take too much ribavirin capsules, call your health care provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

**What are the possible side effects of ribavirin capsules?**

**Ribavirin capsules may cause serious side effects, including:**

**See “What is the most important information I should know about ribavirin capsules?”**

- **Swelling and irritation of your pancreas (pancreatitis).** You may have stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Your mouth may be very dry, which can lead to problems with your teeth and gums.
- **Severe blood disorders.** An increased risk when used in combination with azathioprine.
- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with INTRON A. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with ribavirin capsules and INTRON A.
- **Severe depression.**
- **Thoughts of hurting yourself or others, and suicidal attempts.** Adults and children who take ribavirin capsules, especially teenagers, are more likely to have suicidal thoughts or attempt to hurt themselves while taking ribavirin capsules. Call your health care provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about hurting yourself or others or dying.

**Tell your health care provider right away if you have any side effect that bothers you or that does not go away.**

**The most common side effects of ribavirin capsules include:**

- flu-like symptoms - feeling tired, headache, shaking along with high temperature (fever), nausea, and muscle aches.
- mood changes, feeling irritable.

**The most common side effects of ribavirin capsules in children include:**

- a decrease in the blood cells that fight infection (neutropenia).
- a decrease in appetite.
- stomach pain and vomiting.

Tell your health care provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ribavirin capsules. For more information ask your health care provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **How should I store ribavirin capsules?**

- Store **ribavirin capsules** between 15° to 30°C (59° to 86°F).

**Keep ribavirin capsules and all medicines out of the reach of children.**

#### **GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF RIBAVIRIN CAPSULES.**

It is not known if treatment with ribavirin capsules will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking ribavirin capsules will prevent you from infecting another person with the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ribavirin capsules for a condition for which it was not prescribed. Do not give ribavirin capsules to other people, even if they have the same symptoms that you have. They may harm them.

This Medication Guide summarizes the most important information about ribavirin capsules. If you



would like more information, talk with your health care provider. You can ask your pharmacist or health care provider for information about ribavirin capsules that is written for health professionals.

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

### **What are the ingredients in ribavirin capsules?**

**Active ingredient:** ribavirin

**Inactive ingredients:** microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

Intron A is a registered trademark of Schering Corporation.

VIDEX® is a registered trademark of Bristol-Myers Squibb Company.

Manufactured for:

**Aurobindo Pharma USA, Inc.**

2400 Route 130 North

Dayton, NJ 08810

Manufactured by:

**Aurobindo Pharma Limited**

Hyderabad-500 090, India

Revised: 07/2015

### **PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 200 mg (500 Capsule Bottle)**

**NDC 65862-290-05**


**Ribavirin Capsules**

**200 mg**

**PHARMACIST: Dispense the accompanying Medication Guide to each patient.**

**Rx only            500 Capsules**

**AUROBINDO**



3  
N  
65862-290-05  
2


**Each capsule contains:**  
Ribavirin USP 200 mg.

**Usual Dosage:** See product information.

**Read accompanying directions carefully.**

**Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].**

**AVOID PREGNANCY WHILE TAKING THIS MEDICATION. READ THE MEDICATION GUIDE FOR IMPORTANT INFORMATION.**



**For combination use with INTRON® A (Interferon alfa-2b, recombinant) Injection\***

\* INTRON® A is a registered trademark of Schering Corporation


NDC 65862-290-05

**Ribavirin Capsules USP**

**200 mg**

**PHARMACIST: Dispense the accompanying Medication Guide to each patient.**

**Rx only            500 Capsules**



Manufactured for:  
**Aurobindo Pharma USA, Inc.**  
2400 Route 130 North  
Dayton, NJ 08810

Manufactured by:  
**Aurobindo Pharma Limited**  
Hyderabad-500 090, India

M.L.No.: 19/HD/AP/95/F/R

P 14 13 778

Batch:

Expiry:

RIBAVIRIN

ribavirin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:65862-290
Route of Administration	ORAL	DEA Schedule	

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
RIBAVIRIN (UNII: 49717AWG6K) (RIBAVIRIN - UNII:49717AWG6K)	RIBAVIRIN	200 mg

Inactive Ingredients	
Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONE K30 (UNII: U725QWY32X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
GELATIN (UNII: 2G86QN327L)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	WHITE	Score	no score
Shape	CAPSULE	Size	19mm
Flavor		Imprint Code	E;81
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:65862-290-42	42 in 1 BOTTLE; Type 0: Not a Combination Product		
2	NDC:65862-290-56	56 in 1 BOTTLE; Type 0: Not a Combination Product		
3	NDC:65862-290-70	70 in 1 BOTTLE; Type 0: Not a Combination Product		
4	NDC:65862-290-84	84 in 1 BOTTLE; Type 0: Not a Combination Product		
5	NDC:65862-290-18	180 in 1 BOTTLE; Type 0: Not a Combination Product		
6	NDC:65862-290-05	500 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079117	09/17/2009	

**Labeler** - Aurobindo Pharma Limited (650082092)

Establishment				
Name	Address	ID/FEI	Business Operations	

Aurobindo Pharma Limited		918917642	ANALYSIS(65862-290) , MANUFACTURE(65862-290)
--------------------------	--	-----------	--

Establishment			
Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917647	API MANUFACTURE(65862-290)